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Chlordimeform Effects on Schedule-Controlled Behavior in Rats

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16. ABSTRACT

Chlordimeform (CDMF) is a member of a relatively new class of insecticide/acaricide, the formamidines, which has rather unique effects. Unlike the widely used organophosphate and carbamate insecticides, CDMF does not appear to inhibit cholinesterases, and intoxication is not accompanied by signs of cholinergic over-stimulation [3,15]. On the contrary, the available evidence suggests that one of the many actions of CDMF may be on monoamine-containing neurons in the central nervous system. CDMF in rats has been shown in vitro to inhibit hepatic monoamine oxidase and in vivo to increase whole-brain levels of 5-hydroxytryptamine (5-HT) and norepinephrine [3]. In addition, some behavioral effects seen after large dosages have been reported to resemble those obtained after administration of agents which effect neuronal release of 5-hydroxytryptamine, either p-chloroamphetamine alone or l-tryptophan in combination with a monoamine oxidase inhibitor [3,19].

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Chlordimeform Effects on Schedule-Controlled Behavior in Rats[1]

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MacPHAIL, R. C. AND J. D. LEANDER. *Chlordimeform effects on schedule-controlled behavior in rats.* NEUROBEHAV. TOXICOL. TERATOL. 3(1) 19–26, 1981.—Eight food-deprived rats were trained to perform under a schedule that arranged milk reinforcement after every 10 (N=4) or 40 (N=4) lever presses. Baseline control performance for all rats was characterized by a brief pause in responding after milk delivery, followed by a rapid rate of responding that was maintained until the next milk delivery. Chlordimeform HCl (CDMF) produced dose-related decreases in response rate and increases in pause duration when 1.25–40 mg/kg body weight was given IP, 10 min pre-session. Dosages estimated to produce a 50% decrease in overall responding were between 5 and 10 mg/kg for rats performing under either response requirement. Similar effects on performance were obtained when 5 mg/kg CDMF was given 10 and 50 min pre-session, and when 10 mg/kg was given 10, 50, and 120 min pre-session. The effect of 5 mg/kg CDMF (10 min pre-session) was not consistently modified by prior monoamine oxidase inhibition with pargyline HCl (20 or 50 mg/kg, 60 min pre-session). CDMF (10 mg/kg) also decreased the rate at which rats (N=5) responded, and increased the rate of shock delivery, under a signaled shock avoidance paradigm.

Chlordimeform Pesticide Operant behavior Rats

CHLORDIMEFORM (CDMF) is a member of a relatively new class of insecticide/acaricide, the formamidines, which has rather unique effects. Unlike the widely used organophosphate and carbamate insecticides, CDMF does not appear to inhibit cholinesterases, and intoxication is not accompanied by signs of cholinergic over-stimulation [3,15]. On the contrary, the available evidence suggests that one of the many actions of CDMF may be on monoamine-containing neurons in the central nervous system. CDMF in rats has been shown *in vitro* to inhibit hepatic monoamine oxidase and *in vivo* to increase whole-brain levels of 5-hydroxytryptamine (5-HT) and norepinephrine [3]. In addition, some behavioral effects seen after large dosages have been reported to resemble those obtained after administration of agents which effect neuronal release of 5-hydroxytryptamine, either *p*-chloroamphetamine alone or *l*-tryptophan in combination with a monoamine oxidase inhibitor [3,19].

Very little additional data are available on the behavioral effects of CDMF, except that CDMF produces flavor aversions [13] and increases food intake in rats [18], and alters schedule-controlled performance in pigeons [11]. In the present experiment, therefore, the effects of varying dosages and treatment times of CDMF were determined on the performance of rats under a schedule of milk reinforcement (milk-reinforcement experiments) or an electric-shock-postponement schedule (shock-avoidance experiments). Schedule-controlled performance was chosen because of its proven sensitivity in the study of drug effects and of alterations in neurotransmitters within the central and peripheral nervous system (e.g., [16,21]), and because of its demonstrated generality across species [16]. The effects of chlordimeform were studied on avoidance behavior because of the report that animals receiving chlordimeform could be aroused from heavy sedation to respond without ataxia [15], a pattern associated with antipsychotic drugs on signaled-avoidance baselines [16].

METHOD

Animals. For the milk-reinforcement experiments, eight male Sprague-Dawley-derived (CD) rats were received from

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Charles River Breeding Company at 90 days of age, and were housed individually throughout the experiment. The rats were allowed to acclimate to the colony room and the 12-hr on, 12-hr off lighting cycle that began at 0600 hr. The rats were then reduced in body weight through food deprivation until they weighed approximately 520 g, which was approximately 70% of the weight of a comparable group of rats (N=11) receiving unlimited access to food, and were maintained at this weight for the remainder of the experiment. Water was available freely in the home cage and in the transport cages in which each rat was housed for 3.5 to 4.0 hr each day.

For the shock-avoidance experiments, the rats (N=5) were Long-Evans-derived hooded males approximately 100 days old at the start; food and water were freely available except during test sessions.

Apparatus. For the milk-reinforcement experiments testing was carried out in four commercial chambers (Coulbourn Instrument Co., Model E10-10) measuring 30×24×29 cm. Each was equipped with a response lever (No. E21-03, operated by a force of 0.3 N) on the left side of the front panel and 2.5 cm above the grid floor, a centrally located house light (1.1 W), and a mechanism on the right (E14-06) that was modified for delivery of 50 μl of fluid. Each test chamber was contained within a larger ventilated enclosure that was sound- and light-attenuating. Contingencies were arranged and data were collected using solid state programming equipment (Coulbourn Instruments Co.) that was located in an adjacent room.

For the shock-avoidance experiments the chamber (Lehigh Valley Electronics) measured 31×25×27 cm and contained a floor grid of 1/2 cm-wide bars spaced 2 cm apart, a response lever (R. Gerbrands Co., 0.3 N) placed on one wall 11 cm above the grid floor, and 2 houselights (3 W) located above the clear plastic ceiling of the test chamber and a light (3 W) over the response lever. Scrambled electric shock (1.4 mA) was delivered to the chamber through the grid.

Behavioral procedure. Each rat to be used for the milk-reinforcement experiments was adapted to a restricted food regimen and then was trained to press the response lever using a modification of the auto shaping procedure first described for pigeons [4]. Once the lever-pressing response was trained, the schedule of milk reinforcement was changed so that under the final conditions, milk presentation was contingent on the completion of ten responses (fixed-ratio or FR 10) for four rats and 40 responses (FR 40) for the other four rats. Sessions were signaled by illumination of the houselight. Reinforcement consisted of presentation of 50 μl of a solution of 2 parts tap water to one part Borden's Eagle Brand sweetened condensed milk. Milk presentation was accompanied by extinguishing the houselight of the test chamber and illumination of a lamp located above the dipper for four seconds, during which responses had no programmed consequences. Sessions were arranged Monday through Friday, at the same time each day (between 0900 and 1400 hr) for each rat. Sessions terminated with either the first reinforcement after 45 min or after an additional 3 min had elapsed, whichever occurred first.

For the shock-avoidance experiments, the rats were trained to lever press under a signaled shock-postponement schedule [9]. In the absence of responding, shocks (1-sec duration) were programmed to occur every 10 sec (shock-shock interval=10 sec). Each response postponed shock delivery for 30 sec (response-shock interval=30 sec). The houselights (a preshock signal) were illuminated 18 sec after the last response and remained illuminated until a response was made. A response during shock presentation terminated houselight illumination and shock immediately. Sessions were conducted Monday through Friday and lasted for 60 minutes. The lamp over the response lever was lit throughout the 60-min session.

Chemical procedures. Once behavioral performances had stabilized, the effects of chlordimeform were determined. Chlordimeform HCl (donated by Noram Agricultural Products, Woodstock, IL) was dissolved in isotonic saline solution, prepared fresh each day before use, and administered IP (1 ml/kg body weight) in dosages of 1.25–40.0 mg of the salt/kg body weight. Treatments were ordinarily given on Tuesdays and Fridays, with Thursday's data representing control performance against which treatments were evaluated. Dose-effect data were first collected, with the dosages of CDMF being administered in an irregular sequence, 10 min pre-session. The saline vehicle was also given alone (1 ml/kg) as a control for the injection procedure. Subsequently, in the milk-reinforcement experiments, three other manipulations were also studied. The first was to determine the effect of different treatment times. The 10 mg/kg dosage was administered either 10, 50 or 120 min pre-session, and 5 mg/kg was given either 10 or 50 min pre-session. These determinations also included treatment with saline vehicle at the appropriate pre-session times.

The second manipulation was to determine the effect of pretreatment with pargyline, since CDMF has been reported to be a monoamine oxidase inhibitor. If CDMF's behavioral effects were due to monoamine oxidase inhibition, it would be expected that pretreatment with pargyline would potentiate those effects. Rats were treated with pargyline HCl (obtained through Sigma Chemical Co., St. Louis, MO 63178), dissolved in normal saline and administered IP (1 ml/kg) in dosages of 20 or 50 mg/kg, one hr prior to the session. The pargyline dosages and times were chosen to maximally affect both forms of MAO [5]. Chlordimeform (5 mg/kg) or saline was then administered 10 min prior to the session.

The third manipulation was to determine the effect of daily administration of CDMF. Arbitrarily selected rats (N=4) were dosed with 10 mg/kg daily for 5 days, whereas other rats (N=2) received the saline vehicle daily. Two of the FR 10 rats died of undetermined causes prior to this phase of the experiment. Finally, after several additional weeks without dosing, redeterminations were made of a portion of the CDMF dose-response function in a manner similar to that already described.

In the shock-avoidance experiment, CDMF (1.25–10 mg/kg) was administered as described above for the acute dose-effect curves in the rats performing under the FR schedules, except that the rats were placed in the darkened test chambers for the 10 min prior to testing.

Data analysis. For the milk-reinforcement procedure, the average overall rate of responding was computed in responses per second from digital counters and elapsed time meters for each rat. Also, the average log latency to initiate responding after milk presentation (the post-reinforcement pause time) was calculated for each rat. The sustained rate ("running rate") was also calculated. This is the rate of responding once responding has been initiated [responses÷(total time minus pause time)]. The control data during the dose-effect and time-course determinations for these dependent variables are shown in Table 1. Additional control

TABLE 1

NON-INJECTION CONTROL PERFORMANCE

	Rat No.	N	Overall Rate (resp/sec)	Sustained Rate (resp/sec)	Pause Duration (log sec)
FR 10	15	20	0.37 ± 0.03	1.96 ± 0.13	1.35 ± 0.04
	33	10	0.73 ± 0.07	3.26 ± 0.42	1.02 ± 0.06
	38	21	1.41 ± 0.09	2.80 ± 0.11	0.56 ± 0.05
	42	21	1.23 ± 0.06	3.08 ± 0.09	0.71 ± 0.04
	Mean		0.94	2.77	0.91
FR 40	17	19	1.24 ± 0.09	2.18 ± 0.09	1.09 ± 0.03
	21	19	5.16 ± 0.32	7.54 ± 0.11	0.33 ± 0.01
	25	20	1.65 ± 0.08	2.41 ± 0.14	0.93 ± 0.04
	40	20	0.81 ± 0.07	1.53 ± 0.09	1.39 ± 0.06
	Mean		2.22	3.42	0.94

Each value represents the mean (± SEM) control performance for each rat during the dose-effect- and time-course-determination phases of the experiment. Also shown are group averages. N=Number of sessions on which control data were determined.

values are given in the figure legends. The effects of chlordimeform are shown in most figures as means of groups of rats calculated as a percent of each animal's control value. The pause time data were calculated as mean log values. Percent-of-control data are plotted for log pause duration. tion.

For the shock-avoidance procedure, average rates of responding in responses per minute and average shock rates in shock per minute were calculated from digital counters and elapsed time meters. The frequencies of different interresponse times (IRTs) were collected in 3-sec class intervals. These frequencies were then converted to Anger's interresponse-time-per-opportunity (IRT/OP) measure [1]. The IRT/OP is a conditional probability measure of interres-

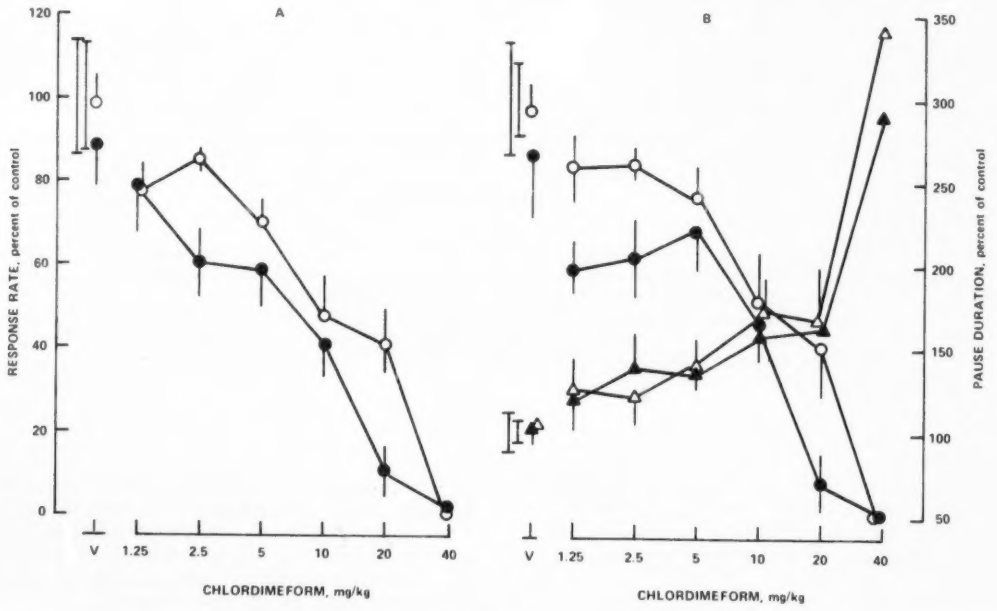

FIG. 1. Effects of chlordimeform on fixed-ratio-reinforced performance in rats. Each symbol in panel A represents the mean effect of at least single determinations of the saline vehicle (V) or a dosage of chlordimeform on the overall response rate of rats performing under FR 10 (●, N=4) or FR 40 (○, N=4), except the largest dosage which was given to only one rat in each FR group. Vertical bars represent ± 1 SEM and brackets at the far left represent ± 2 SEM for non-injection control performance (FR 10 data are displaced to the left of FR 40 data). Each symbol in panel B represents comparable data for sustained response rate (●, ○) and log pause duration (▲, △). Control values (100%) are given in Table 1. CDMF effects exceeding the control brackets were considered significant at the 0.05 level.

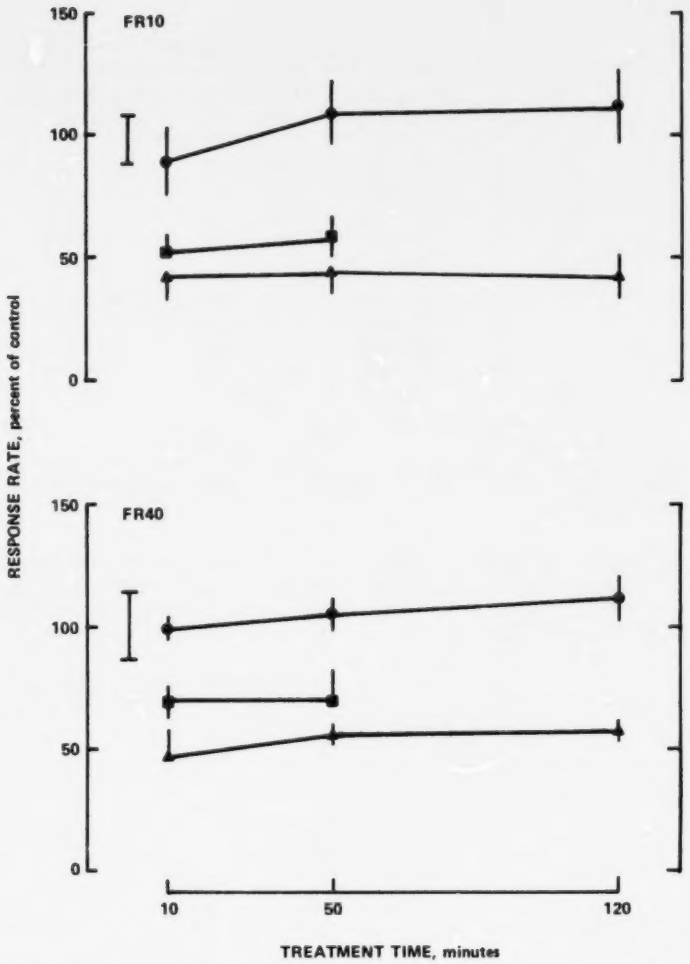

FIG. 2. Time course for the effects of chlordimeform on overall response rates maintained by fixed-ratio reinforcement. Each symbol in the upper panel represents the mean effect ± 1 SEM of at least single determinations of the saline vehicle (●) or of 5 mg/kg (■) or 10 mg/kg (▲) of chlordimeform on the performance of rats under FR 10 (N=4); vertical bars at far left represent ± 2 SEM for control performance. The lower panel represents comparable data for rats (N=4) performing under FR 40. See legend for Fig. 1 for additional details.

ponse interval frequencies and is computed by dividing the number of IRTs within a class interval by the number of opportunities (OP) for that IRT to occur. The number of opportunities is the number of IRTs of that duration or greater.

RESULTS

Control performance in the milk-reinforcement procedure. For each rat, performance under baseline non-injection control conditions was characterized by a pause after each milk delivery (post-reinforcement pause) followed by a rapid rate of responding that was maintained (sustained rate) until the next milk delivery. Control values are given for individual rats in Table 1. In general, there were no differences in performance due to the particular schedule requirement under which the rats performed. The one exception was R 21 which under FR 40 had the most rapid rate of responding and the shortest pause duration of all the rats.

Effects of chlordimeform in milk-reinforcement procedure. When given 10 min prior to testing, chlordimeform produced dose-related decreases in the overall response rates in all rats (Fig. 1A). These decreases in overall rates of responding were due to both an increase in pause duration and a decrease in rate of responding once it was initiated (Fig. 1B). Although the decreases in responding were slightly

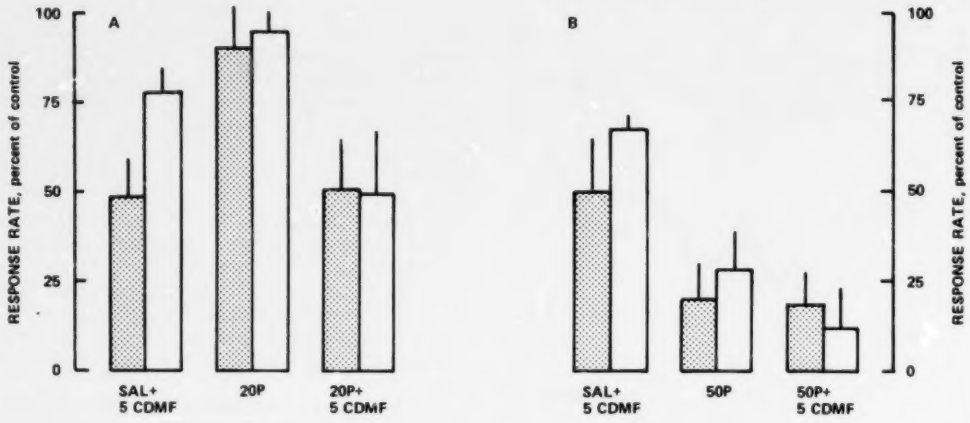

FIG. 3. Effects of pargyline (P) given alone and in combination with chlordimeform (CDMF) on fixed-ratio performance. Panel A shows the effect of single determinations of P (20 mg/kg), CDMF (5 mg/kg) and their combination on the overall response rates of rats performing under FR 10 (N=3, stippled columns) or under FR 40 (N=4, open columns). Vertical bars represent 1 SEM. Control values (100%), based on 3–4 control sessions for each rat, are 1.09 responses per second (FR 10) and 2.48 responses per second (FR 40). Panel B shows comparable data for the effect of 50 mg/kg pargyline alone and in combination with CDMF. Control values (100%) are 1.15 responses per second (FR 10) and 2.43 responses per sec (FR 40), and are based on data from 3–4 control sessions for each rat.

greater for rats performing under FR 10, the dosages estimated to reduce responding by 50% were comparable for both groups (between 5 and 10 mg/kg); no differences due to schedule requirement were apparent in CDMF's effects on pause duration.

The decreases in overall responding produced by CDMF were comparable when 5 mg/kg was given 10 or 50 min prior to testing, and when 10 mg/kg was given 10, 50 or 120 min prior to testing (Fig. 2). Similar constancies were obtained for the effect of CDMF on pause duration and on response rate once responding was initiated, and are therefore not presented.

Pargyline pretreatment. Treatment of the rats with 20 mg/kg of pargyline did not appreciably disrupt responding under FR 10 or FR 40, and did not modify the subsequent effect of 5 mg/kg CDMF on performance (Fig. 3A). A larger dosage of pargyline (50 mg/kg) substantially reduced responding when given by itself. When given in combination with CDMF (5 mg/kg), however, the reduction in responding did not differ from that produced by pargyline alone (Fig. 3B). These changes in overall response rate were due to effects both on pause duration and on responding once it was initiated (data not shown), and were not systematically related to the schedule requirement under which the rats performed.

Repeated administration of CDMF. Four of the rats (R 15, 17, 38, 40) were arbitrarily selected to receive daily CDMF (10 mg/kg) for 5 days whereas two rats (R 21, R 25) received the saline vehicle for a comparable period. The results of this phase of the experiment are shown in Fig. 4. Evidence for a progressive diminution of the effect of CDMF on overall rates of responding (i.e., tolerance) was obtained only for R 17, whereas the other three rats did not exhibit a diminution in effect across the days of repeated administration. Rates of responding quickly returned to control levels once daily treatment with CDMF was discontinued.

Redetermination of the effects of CDMF. At the conclusion of this experiment, redeterminations were made of the effects of selected dosages of CDMF (2.5–10 mg/kg) as a check on the long-term integrity of the functions presented in Fig. 1. There was no difference between the effects of CDMF in the two surviving rats performing under FR 10 and those originally determined except that 5 mg/kg produced less suppression (80% of control) than it did initially (59%). For those performing under FR 40, CDMF produced slightly greater behavioral effects during the redeterminations due to both a slightly greater increase in pause duration and decrease in responding once it was initiated (not shown).

CDMF effects on shock avoidance. Low doses of CDMF (1.25–5 mg/kg) did not affect the performance of rats under a signaled shock avoidance procedure. At 10 mg/kg, however, response rate decreased slightly and the rate of shock delivery increased substantially (Fig. 5A and B). The increase in shock rate was due to a systematic decrease in the conditional probability of responding in the presence of the stimulus preceding shock delivery (Fig. 6). As can also be seen in this figure, CDMF did not disrupt the very low probability of responding in the absence of the pre-shock signal.

DISCUSSION

Chlordimeform produced dose-related decreases in the overall rate at which rats responded under fixed-ratio schedules of milk delivery. These decreases were due to both an increase in duration of the pause that ordinarily followed milk delivery, and a decrease in the rate of responding once it was initiated. Complete suppression of responding was obtained at 20–40 mg/kg, depending on the rat. CDMF (10 mg/kg) also decreased the responding of rats under a signaled shock-avoidance procedure and dramatically in-

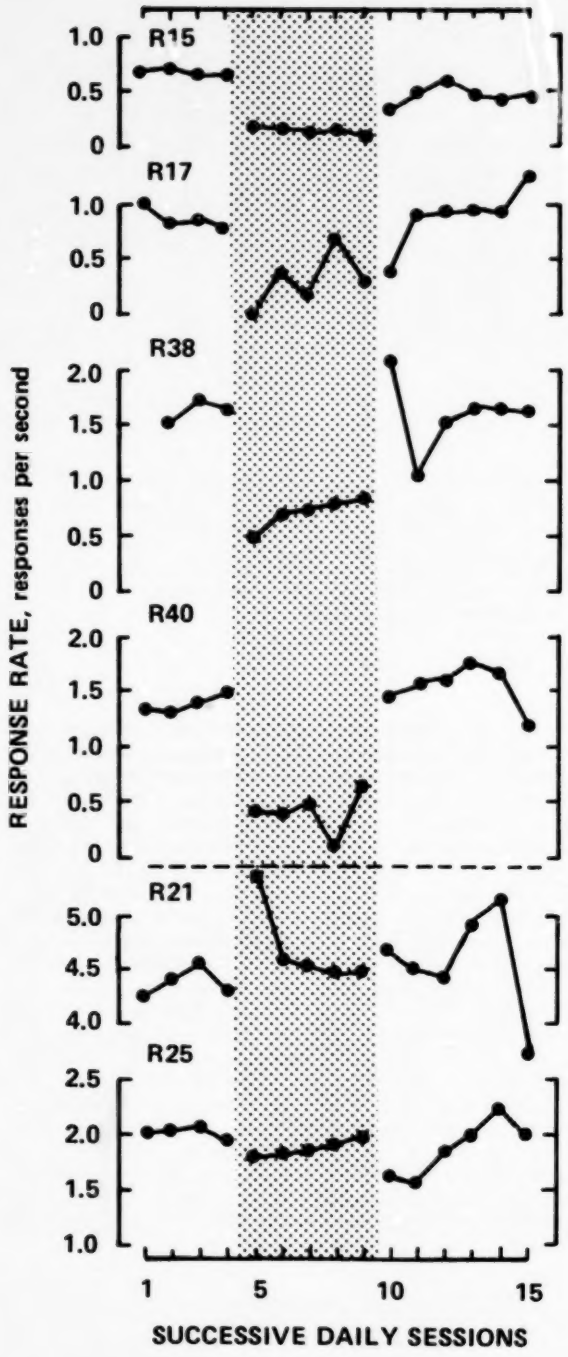

FIG. 4. Effect of daily administration of 10 mg/kg CDMF (top four panels) or saline (bottom two panels) on fixed-ratio-reinforced overall response rates. CDMF or saline were administered for the five intermediate sessions marked by the stipled bar. No treatments were administered prior to or subsequent to these five sessions. Note the restricted scales for the two rats receiving saline.

creased the rate of shock delivery. The fact that the 10 mg/kg dose of CDMF reduced both food-maintained and shock-avoidance responding indicates that the behavioral effects of CDMF are probably not due to an indirect effect on feeding motivation as might be hypothesized from earlier studies of chlordimeform [18]. The dose range over which CDMF produced these behavioral effects is in close agreement with that previously shown to alter food intake in rats [18], induce flavor aversions in rats [13], and disrupt schedule-controlled performance in pigeons [11]. Moreover, except at dosages that completely suppressed responding, changes in performance were not accompanied by overt signs of intoxication. Since the LD50 of CDMF (IP) in rats has been reported to be between 123 mg/kg [20] and 300 mg/kg [6], these data indicate that CDMF has prominent behavioral effects at dosages substantially below those producing lethality or overt toxicity.

In the present experiment the disruption in schedule-controlled performance was comparable regardless of whether CDMF was given 10 or 120 min prior to testing. By the same token, the effects of CDMF on the schedule-controlled performance of pigeons were the same when CDMF was given 10 min prior to testing by either the IM or PO routes [11]. Chlordimeform is rapidly eliminated from orally dosed rats; approximately 90% of the dosage is eliminated in the urine within 24 hr [8]. Metabolism of CDMF first involves demethylation to form nor-chlordimeform, and there is evidence that this demethylated derivative has considerable biological activity [2, 7, 18]. These data suggest that it is unlikely that the changes in schedule-controlled performance were due to the demethylated metabolite of CDMF rather than to CDMF itself.

Very little is known about the mechanism(s) by which CDMF produces its behavioral effects. Unlike many other types of insecticides, formamidines do not inhibit cholinesterases [3]. Formamidines, however, have been shown *in vitro* to inhibit monoamine oxidase [2] and to increase *in vivo* whole brain levels of 5-hydroxytryptamine (5-HT) and, to a lesser extent, norepinephrine [3]. Moreover, the behavioral syndrome produced by large dosages of CDMF has been reported to resemble that produced by 5-HT agonists [19]. However, the possibility of monoaminergic involvement in the effects of CDMF on schedule-controlled behavior was not supported by the present results since the combined effects of CDMF and pargyline were not different from those produced by CDMF alone (when 20 mg/kg pargyline was administered) or by pargyline alone (when 50 mg/kg was administered). A strong conclusion regarding monoamine involvement and the role of monoamine oxidase inhibition in the behavioral effects of CDMF must await more extensive research using a variety of neuropharmacological tools and wide dosage ranges.

When CDMF (10 mg/kg) was administered daily, evidence for tolerance to its effects was obtained in only one of four rats. In contrast to this, tolerance developed rapidly to the rate-decreasing effect of CDMF when administered daily to pigeons [11]. Of course, it is possible that tolerance would have developed in the present experiment had the daily dosing been continued for a longer time. The data do, however, highlight the importance of using multiple species in comprehensively evaluating the behavioral impact of toxic chemicals [10].

Schedule requirement did not seem to appreciably influence the effects of CDMF on performance, in contrast to what has been reported for other psychoactive substances

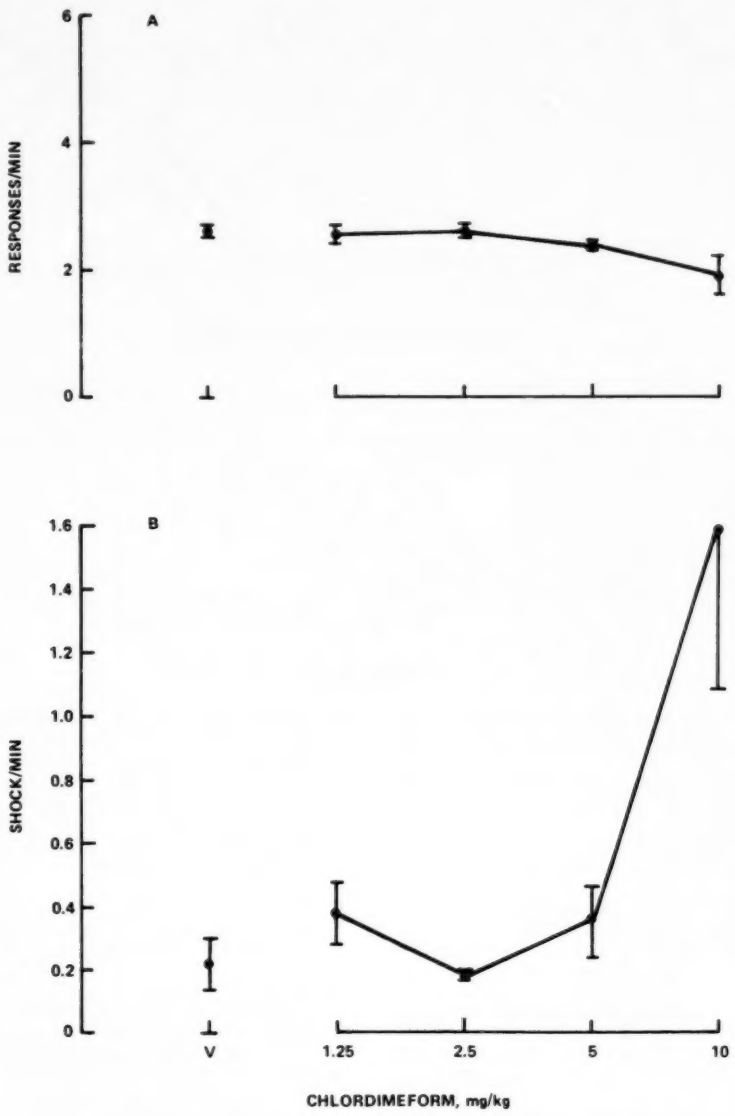

FIG. 5. Effects of CDMF on performance under the signaled shock-avoidance procedure. Each symbol in panel A represents the mean effect (± 1 SEM) of single determinations of the saline vehicle (V) or a dosage of CDMF (1.25 – 10 mg/kg) on the response rate of a group of 5 rats. Symbols in panel B represent comparable data for the rate of shock delivery.

[12, 14, 16, 17]. It would be premature, however, to conclude that schedule parameters are not determinants of CDMF's behavioral effects until a wider range of values and schedules have been explored using individual organism experimental designs (cf. [22]).

The large increase in shock rate without a large parallel decrease in response rate after 10 mg/kg of chlordimeform, along with a decrease in the conditional probability of a response during the preshock stimulus, suggests that chlordimeform produces an effect on signaled avoidance similar to antipsychotic agents [16]. This is compatible with the findings in pigeons responding under multiple schedules of reinforcement, where chlordimeform decreased responding under the fixed-interval schedule at lower doses than responding under the fixed-ratio schedule; again, a pattern characteristic of antipsychotic drugs [16]. These data from

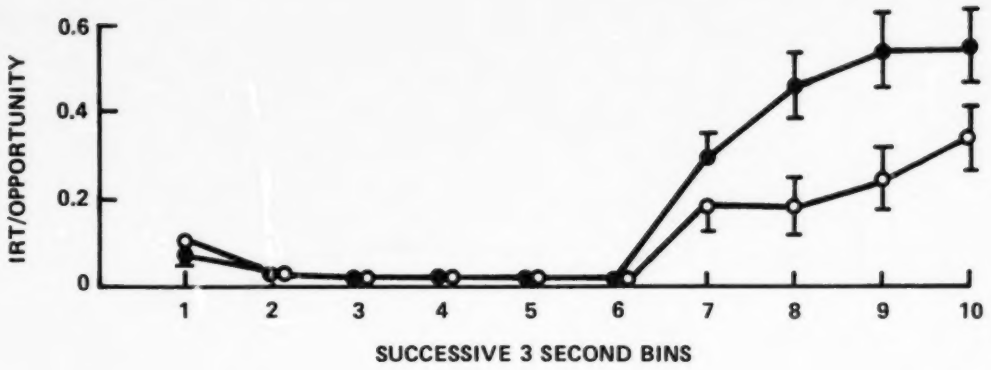

FIG. 6. Effects of CDMF (10 mg/kg) on the conditional probability of responding under the signaled shock-avoidance procedure. Each symbol represents the mean ± 1 SEM for 5 rats of the effect of CDMF (○—○) or of the saline vehicle (●—●). Onset of the pre-shock stimulus occurred at the beginning of the sixth 3-sec bin and remained on until a response was made. Shock delivery occurred after the 10th 3-sec bin.

two species (rat and pigeon) suggest that chlordimeform's behavioral effects are similar to the behavioral effects of antipsychotic drugs. Future research will further evaluate this hypothesis.

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REFERENCES

1. Anger, D. The dependence of interresponse times upon the relative reinforcement of different interresponse times. *J. exp. Psychol.* **52:** 145–161, 1956.
2. Aziz, S. A. and C. O. Knowles. Inhibition of monoamine oxidase by the pesticide chlordimeform and related compounds. *Nature* **242:** 417–418, 1973.
3. Beeman, R. W. and F. Matsumura. Chlordimeform: A pesticide acting upon amine regulatory mechanisms. *Nature* **242:** 273–274, 1973.
4. Brown, P. L. and H. M. Jenkins. Autoshaping of the pigeon's key peck. *J. exp. Analysis Behav.* **11:** 1–8, 1968.
5. Corte, L. D. and K. F. Tipton. The turnover of the A- and B-forms of monoamine oxidase in rat liver. *Biochem. Pharmac.* **29:** 891–895, 1980.
6. Hollingworth, R. M. Chemistry, biological activity, and uses of formamidine pesticides. *Envir. Hlth. Perspect.* **14:** 57–69, 1976.
7. Hollingworth, R. M. and L. L. Murdock. Formamidine pesticides: Octopamine-like actions in a firefly. *Science* **208:** 74–76, 1980.
8. Knowles, C. O. and A. K. S. Gupta. N′-(4-chloro-*O*-tolyl)-N,N-dimethylformamidine-^{14}C(Galecron) and 4-chloro-*O*-toluidine-^{14}C-metabolism in the white rat. *J. Econ. Ent.* **63:** 856–859, 1970.
9. Leander, J. D. Effects of promazine, chlorpromazine, *d*-amphetamine, and pentobarbital on treadle pressing by pigeons under a signaled shock-postponement schedule. *J. exp. Analysis Behav.* **26:** 361–368, 1976.
10. Leander, J. D. The need for comparative neurotoxicology. *Neurotoxicology* **1:** 693–694, 1980.
11. Leander, J. D. and R. C. MacPhail. Effect of chlordimeform (a formamidine pesticide) on schedule-controlled responding of pigeons. *Neurobehav. Toxicol.* **2:** 315–321, 1980.
12. MacPhail, R. C. Rate-dependent effects of *d*-amphetamine are also schedule dependent. *Proc. of 79th APA Convention,* 753–754, 1971.
13. MacPhail, R. C. and J. D. Leander. Flavor aversions induced by chlordimeform. *Neurobehav. Toxicol.* **2:** 363–365, 1980.
14. MacPhail, R. C. and L. S. Seiden. Modulation by response requirements of the effects and interactions of *d*-amphetamine and α-methyl-*p*-tyrosine on the schedule-controlled performance of rats. *Fedn Proc.* **35:** 785, 1976.
15. Matsamura, F. and R. W. Beeman. Biochemical and physiological effects of chlordimeform. *Envir. Hlth. Perspect.* **14:** 71–82, 1976.
16. McMillan, D. E. and J. D. Leander. Effects of drugs on schedule-controlled behavior. In: *Behavioral Pharmacology,* edited by S. D. Glick and J. Goldfarb. St. Louis: C. V. Mosby, 1976.
17. Morse, W. H. Use of operant conditioning techniques for evaluating the effects of barbiturates on behavior. In: *Psychosomatic Medicine,* edited by J. H. Nodine and J. H. Moyer. Philadelphia: Lea and Febiger, 1962.
18. Pfister, W. R., R. M. Hollingworth and G. K. W. Yim. Increased feeding in rats treated with chlordimeform and related formamidines: A new class of appetite stimulants. *Psychopharmacology* **60:** 47–51, 1978.
19. Pfister, W. R., V. Noland, M. T. Lowy, D. E. Nichols and G. K. W. Yim. Comparison of the behavioral effects of *para*-chloroamphetamine, chlordimeform, quipazine, and intraventricular serotonin in the rat. *Communs Psychopharmacol.* **2:** 287–296, 1978.
20. Robinson, C. P., P. W. Smith, J. D. Zelenski and B. R. Endicott. Lack of an effect of interference with amine mechanisms on the lethality of chlordimeform in the rat. *Toxic. appl. Pharmac.* **33:** 380–383, 1975.
21. Seiden, L. S. and L. A. Dykstra. *Psychopharmacology: A Biochemical and Behavioral Approach.* New York: Van Nostrand Reinhold, 1977.
22. Sidman, M. *Tactics of Scientific Research.* New York: Basic Books, 1960.